Remarks

Claims 30-36 are pending, and new claims 39-52 have been added. By this amendment, Applicants have canceled, without prejudice or disclaimer, claims 1, 5-11, 19-21, and 37-38. Applicants reserve the right to pursue the canceled claims in a divisional or continuation application(s).

Applicants have amended claim 30 to recite "wherein ritonavir in said pharmaceutical composition has markedly improved dissolution rate in 0.1 N HCl at 37°C as compared to neat ritonavir." This amendment is supported at least by Example 1 and Figure 2 of the specification.

Applicants have also amended claim 35 to delete the term "further."

Applicants have added claims 39-52. Claim 39 is supported at least by page 9, lines 14-19, of the specification. Claim 40 is supported at least by page 9, lines 3-6, of the specification. Claims 41-42 are supported at least by page 6, lines 13-16, of the specification and original claims 19-21. Claim 43 is supported at least by Example 1 and pages 8-11 of the specification and original claims 1-11. Claims 44-45 are supported at least by pages 9-10 of the specification and original claims 9-10. Claims 46-47 are supported at least by Example 1 and page 8, lines 6-17, of the specification. Claim 48 is supported at least by original claim 8. Claim 49 is supported at least by page 9, lines 14-19, of the specification. Claim 50 is supported at least by page 9, lines 3-6, of the specification. Claims 51-52 are supported at least by page 6, lines 13-16, of the specification and original claims 19-21.

In addition, Applicants have amended the specification to correct two obvious errors. Specifically, Applicants have replaced the phrase "(molecular)" in the paragraph starting at page 8, line 6, and the phrase "(molecular dispersion)" in the paragraph starting at page 8, line 18, with "(e.g., molecular)" and "(e.g., molecular dispersion)," respectively. As described on pages 2-3 of the specification, "[t]he term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (or fusion), solvent, or melting-solvent methods. (Chiou and Riegelman, *Journal of Pharmaceutical Science*, *60*, 1281 (1971))." On pages 1284-1293, Chiou and Riegelman (Exhibit 1) describes various solid dispersion systems including simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, and amorphous precipitation of a drug in a crystalline carrier. Based on the foregoing, Applicants respectfully submit that one of ordinary skill could immediately recognize that the term "solid dispersion," as used in the present application, is not limited to molecule

dispersion. Accordingly, Applicants respectively submit that the addition of "e.g." does not introduce new matter. *See* MPEP 2163.07 ("An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction").

Because the amendments to the specification and claims do not introduce new matter, Applicants respectfully request entry of these amendments.

Claim Rejections Under 35. U.S.C. 112

On page 2, the Office Action rejects claims 1, 5, 7-11, and 19-21 under 35 U.S.C. 112, first paragraph, for failing to satisfy the written description requirement. Applicants have canceled claims 1, 5, 7-11, and 19-21 without prejudice or disclaimer, thereby rendering the rejections of these claims moot. Withdrawal of the rejections of these claims is, therefore, respectfully requested.

Objection to the Claims

On page 3, the Office Action objects to claims 5, 6, and 20 for informalities. Applicants have canceled claims 5, 6, and 20 without prejudice or disclaimer, thereby rendering the objections to these claims moot. Withdrawal of the objections to these claims is, therefore, respectfully requested.

On page 3, the Office Action suggests Applicants amending claim 7. The Office Action also contends that claims 31 and 37, and claims 6, 33 and 38, are identical in scope. Applicants have canceled claims 6-7 and 37-38 without prejudice or disclaimer, thereby addressing the Examiner's concerns.

Claims Rejections Under 35 U.S.C. 102(b)

On pages 3-4, the Office Action rejects claims 30, 31, 35, and 37 under 35 U.S.C. 102(b) as being anticipated by Al-Razzak *et al.* (U.S. Patent No. 5, 610, 193). Applicants respectfully traverse the rejection.

The Office Action contends that column 9, Example 4 and lines 42-64 of Al-Razzak *et al.* teach a solid dispersion comprising ritonavir in PEG 1450. The Office Action also contends that

"because no special steps are taken by Al-Razzak et al to produce its HIV protease inhibitors in crystalline form, the HIV protease inhibitors in the compositions of Al-Razzak et al are deemed inherently to be in amorphous form to the same extent claimed by Applicants."

Applicants respectfully submit that column 9, lines 42-64, of Al-Razzak *et al.* does not teach any solid dispersion of amorphous ritonavir. Column 9, lines 42-64, of Al-Razzak *et al.* describes general procedures of mixing a solution of an HIV protease inhibitor with a pharmaceutically acceptable adsorbent(s). In column 4, lines 49-55, Al-Razzak *et al.* defines "pharmaceutically acceptable adsorbents" as "silicon dioxide, colloidal silicon dioxide (for example, Cab-o-sil®, available from Cabot Corp.), microcrystalline cellulose, starch, maltodextrin, talc, calcium carbonate, pectin, aluminum silicate, crospovidone (for example, Polyplasdone®XL or XL10, available from GAF Corp.) and the like." As appreciated by one of ordinary skill in the art, many of these adsorbents are not water soluble, and the procedures provided in column 9, lines 42-64, of Al-Razzak *et al.* would not produce any solid dispersion of HIV protease inhibitors. Accordingly, Applicants respectfully submit that column 9, lines 42-64, of Al-Razzak *et al.* does not teach any solid dispersion of amorphous ritonavir.

Moreover, Applicants respectfully submit that Example 4 of Al-Razzak *et al.* does not inherently teach any solid dispersion of amorphous ritonavir. As demonstrated by Dr. Law's Declaration (Exhibit 2), the composition of Example 4 of Al-Razzak *et al.* is not likely to be a solid dispersion of amorphous ritonavir. This is because ritonavir prepared according to Al-Razzak *et al.* is crystalline ritonavir. *See* Example 17, 20, and 22 of Al-Razzak *et al.*; Example 1 of U.S. Patent No. 5,541,206 (Exhibit 4); and column 1, lines 39-43, of U.S. Patent No. 6,894,171 (Exhibit 5). Because crystalline ritonavir is practically insoluble in molten PEG 1450, Applicants respectfully submit that a ritonavir molecule in the composition of Example 4 is likely to remain in crystalline form. This is further supported by column 29, Table 1, of Al-Razzak *et al.*, where it is shown that the composition of Example 4 has only 4.2% bioavailability, comparable to that of unformulated or poorly formulated ritonavir in Examples 1-3 and 5-6. In contrast, Figure 2 of the present application shows that a solid dispersion of amorphous ritonavir has markedly improved bioavailability as compared to unformulated ritonavir. Based on all of the above reasons, Applicants respectful submit that the composition of Example 4 of Al-Razzak *et al.* is not likely to be a solid dispersion of amorphous ritonavir.

MPEP 2112 states that "[t]o establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." MPEP also 2112 states that "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient." (Internal citation omitted). As demonstrated above, the composition of Example 4 of Al-Razzak *et al.* is not likely to be a solid dispersion of amorphous ritonavir. Accordingly, Applicants respectfully submit that the Office Action has failed to establish a *prima facie* case of anticipation by inherency. Reconsideration and withdrawal of the 102(b) rejection of claims 30, 31 and 35 are, therefore, respectfully requested.

In addition, Applicants have amended claim 30 to recite "wherein ritonavir in said pharmaceutical composition has markedly improved dissolution rate in 0.1 N HCl at 37°C as compared to neat ritonavir." As noted, the composition of Example 4 of Al-Razzak *et al.* has only 4.2% bioavailability. Figure 3 and Example 1 of the present application show that the *in vitro* dissolution rate correlates well with *in vivo* bioavailability. As a result, the composition of Example 4 of Al-Razzak *et al.* is likely to have poor dissolution in 0.1 N HCl at 37°C. Accordingly, Applicants respectfully submit that Al-Razzak *et al.* does not teach or suggest each and every element of claim 30. *See* MPEP 2131 ("To anticipate a claim, the reference must teach every element of the claim"). Reconsideration and withdrawal of the 102(b) rejection of claim 30 are, therefore, respectfully requested.

Because claims 31 and 35 depend from patentable claim 30, reconsideration and withdrawal of the 102(b) rejection of claims 31 and 35 are also respectfully requested.

Applicants have canceled claim 37 without prejudice or disclaimer, thereby rendering the rejection of claim 37 moot.

Applicants have added new claim 43 which recites a "pharmaceutical composition comprising ritonavir, wherein ritonavir in said composition is formulated as a solid dispersion of amorphous ritonavir in a matrix including a water soluble polymer." As noted, a ritonavir molecule in the composition of Example 4 of Al-Razzak *et al.* is likely to remain in crystalline form. Accordingly, Applicants respectfully submit that Al-Razzak *et al.* does not teach claim 43. Because claims 44-52 depend from claim 43, Applicants respectfully submit that Al-Razzak *et al.* does not teach these claims either.

Claims Rejections Under 35 U.S.C. 103(a)

On page 4, the Office Action further rejects claims 32-33 as being obvious over Al-Razzak *et al.* in view of Sham *et al.* (U.S. Patent No. 5,914,332). Specifically, the Office Action contends that Sham *et al.* teaches the desirability of administering combinations of ritonavir and ABT-378 and that it would have been obvious to one of ordinary skill in the art to include ABT-378 in the composition of Example 4 of Al-Razzak *et al.* Applicants respectfully traverse the rejection.

As discussed above, Al-Razzak *et al.* does not teach or suggest each and every element of claim 30. Claims 32-33 depend from claim 30. Accordingly, Applicants respectfully submit that Al-Razzak *et al.* does not teach or suggest each and every element of claims 32-33. The combination of Sham *et al.* does not remedy this deficiency. *See* MPEP 2143.03 ("To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art"). Accordingly, Applicants respectfully submit that claims 32-33 are not obvious over Al-Razzak *et al.* in view of Sham *et al.*

In addition, as noted above, the composition of Example 4 of Al-Razzak *et al.* has poor bioavailability. Therefore, one of ordinary skill in the art would not have any motivation to add another HIV protease inhibitor to the composition of Example 4. For the same reason, there would be no desirability to administer such a formulation to a patient.

Based on the foregoing, Applicants respectfully submit that Al-Razzak *et al.* and Sham *et al.*, either alone or in combination, do not render claims 32 and 34 obvious. Reconsideration and withdrawal of the 103(a) rejection of these claims are, therefore, respectfully requested.

On pages 4-5, the Office Action rejects claim 36 under 35 U.S.C. 103(a) as being obvious over Al-Razzak *et al.* in view of Franson *et al.* (U.S. Patent No. 6,197,787). The Office Action contends that Franson *et al.* teaches that solid dispersions comprising poorly soluble drug substances can be made into the form of tablets and that it would have been obvious to one of ordinary skill in the art to make the solid dispersion of Example 4 of Al-Razzak *et al.* in the form of a tablet. Applicants respectfully traverse the rejection.

Claim 36 depend from claim 30. For the reasons set forth above, Applicants respectfully submit that Al-Razzak *et al.* and Franson *et al.*, either alone or in combination, do not teach or suggest each and every element of claim 36. Moreover, one of ordinary skill in the art would not have any motivation to compress the composition of Example 4 into a tablet in

view of its poor bioavailability. Accordingly, Applicants respectfully submit that Al-Razzak *et al*. and Franson *et al*. do not render claim 36 obvious. Reconsideration and withdrawal of the 103(a) rejection of claim 36 are, therefore, respectfully requested.

Conclusion

For at least the reasons set forth above, Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly solicited. Although Applicants believe that the fees paid herewith are correct, the Commissioner is hereby authorized to charge any payment deficiency to deposit account number 01-0025 referring to docket number 6488.US.O2.

Should the Examiner believe that anything further is desired in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' representative designated below.

Respectfully submitted,

Date: February 19, 2007

/Xu Zhang/
Xu Zhang
Lim. Rec. No. L0116

ABBOTT LABORATORIES
Telephone: (847) 935-1133
Facsimile: (847) 938-2623